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Virkkula, P.

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P. Virkkula, MD, PhD^{1,*}, E. Penttilä, MD, PhD^{2,3,*} ,
S. I. Vento, MD, PhD¹, J. Myller, MD, PhD⁴, A. Koskinen, MD, PhD¹,
S. Hammarén-Malmi, MD, PhD¹,
A. Laulajainen-Hongisto, MD, PhD¹ , M. Hytönen, MD, PhD¹,
M. Lilja, MD, PhD¹ , J. Numminen, MD, PhD^{5,6},
S. Sillanpää, MD, PhD^{5,6}, J. Sahlman, MD, PhD³, and
S. Toppila-Salmi, MD, PhD^{7,8}

Abstract

Background: Developing tools to identify chronic rhinosinusitis with nasal polyps (CRSwNP) patients requiring surgical treatment would help clinicians treat patients more effectively. The aim of this retrospective cross-sectional study was to identify cut-off values for eosinophil percentage, nasal polyps (NP), and Lund-Mackay (LM) scores that may predict the need for surgical treatment in Finnish CRSwNP patients.

Methods: Data of CRSwNP patients (N = 378) undergoing consultation for ESS in 2001–19 were used. Data was collected from patient records and Lund-Mackay scores were determined from sinus computed tomography scans. The percentage of eosinophils was microscopically evaluated from the polyp samples available (n = 81). Associations were analyzed by Mann Whitney U test, and cut-off values by the area under the receiver operating characteristic curve (AUROC).

Results: ESS was performed to 293 (77.5%) of patients. Polyp eosinophilia was associated significantly with ESS (p = 0.001), whereas peripheral blood eosinophil count, LM- score and endoscopic NP- score were not (p > 0.05). AUROC values (95% CI) for detecting those needing ESS were for polyp eosinophilia 0.71 (0.60–0.83), p = 0.001, for LM score 0.59 (0.50–0.67), p = 0.054; for NP score 0.56 (0.48–0.64), p = 0.17, and for blood eosinophil count 0.68 (0.46–0.90), p = 0.08. With the threshold value of polyp eosinophilia (>25%), the sensitivity and specificity were optimal for detecting the group needing ESS from the group not undergoing ESS. The cut-off value of blood eosinophil count ($>0.26 \times 10^9/L$) had relatively good, yet statistically insignificant (underpowered), predictive potential. Moderate cut-off values were found for endoscopic LM score ($\geq 14/24$) and NP score ($\geq 4/8$).

Conclusions: Polyp eosinophilia (>25%) predicted ESS among Finnish hospital-level CRSwNP patients. A future challenge would be to find less invasive and cost-effective clinical factors predicting uncontrolled CRSwNP.

Keywords

chronic rhinosinusitis, computed tomography, nasal polyp, sinusitis

¹Department of Otorhinolaryngology—Head and Neck surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

²Department of Otorhinolaryngology, University of Eastern Finland, Kuopio, Finland

³Department of Otorhinolaryngology, Kuopio University Hospital, Kuopio, Finland

⁴Department of Otorhinolaryngology, Päijät-Häme Central Hospital, Lahti, Finland

⁵Department of Otorhinolaryngology, University of Tampere, Tampere, Finland

⁶Faculty of Medicine and Life Sciences and Tampere University Hospital, Tampere, Finland

⁷Department of Allergy, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

⁸Haartman Institute, University of Helsinki, Helsinki, Finland

*P. Virkkula and E. Penttilä shared first authorship.

Corresponding Author:

P. Virkkula, MD, PhD, Department of Otorhinolaryngology, Kasarmikatu 11-13, P.O. Box 263, 00029 HUS, Helsinki, Finland.
Email: paula.virkkula@hus.fi



Introduction

Chronic rhinosinusitis (CRS) lowers patients' quality of life substantially¹ and in spite of appropriate guideline-based care CRS is uncontrolled in up to 30–44%.^{1–3} The two phenotypes of CRS, with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP) are thought to have different etiologies^{1,4,5} and they also differ on the degrees of inflammation with type 2 inflammation and eosinophilia being more common in CRSwNP.¹

CRSwNP is a common condition, and its prevalence varies between 1 and 4%.^{6–8} Up to 45% of the CRSwNP patients will develop asthma, and 8–26% cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs) having NSAID-exacerbated respiratory disease (NERD), also called aspirin exacerbated respiratory disease (AERD).^{1,9–11} In the NERD there is found a strong eosinophilic hyperplastic inflammation on the mucosa of the common airways.¹²

Patients with uncontrolled CRS after appropriate medical treatment will usually undergo endoscopic sinus surgery (ESS). Patients with CRSwNP have more often recurrence of disease than CRS patients without nasal polyps, but they seem to benefit from surgery equally.^{2,13–15} Need for revision surgery in CRS has been associated with gender, young adults, smoking, allergic rhinitis (AR), occupational exposure, previous sinus surgery, presence of nasal polyps, need for systemic medication, asthma and NERD.^{16–22}

Factors arising from clinical examination and tests predicting need for surgery or revision surgery in CRS have been widely investigated. Several clinical markers raising the risk of recurrence have been reported: tissue eosinophilia,^{3,23–25} serum eosinophilia,³ high computed tomography (CT) scores,^{1,3,26} higher preoperative endoscopic Lund-Kennedy scores for polyposis,²⁷ radiological inflammatory findings in frontal sinuses¹⁷ and changes in SNOT-22 scoring after surgery.²⁸

Studies in Chinese Hospital population have proposed cut-off values of uncontrolled CRS, such as Lund-Mackay (LM) score of sinus CT scans ≥ 15 of CRS patients³ and tissue eosinophilia $\geq 20\%$ of CRSwNP patients.²⁹ In a study of Chinese CRSwNP patients the optimal cut-off percentage value of nasal polyp eosinophilia was 27% for predicting polyp recurrence in CRSwNP.³⁰ Peripheral blood eosinophilia has shown to be associated with eosinophilic CRSwNP.³¹ Concordant blood eosinophilia ($\geq 0.3 \times 10^9/L$) and tissue eosinophilia ($\geq 10\%$) has shown to be related to a higher likelihood of poor disease control of CRSwNP.²⁹

Yet there is limited knowledge of optimal cut-off values of eosinophilia in other populations, and – generally – of endoscopic nasal polyp (NP) score in uncontrolled CRS. Therefore, the aim of the present study was

to identify cut-off values of nasal polyp eosinophilia, peripheral blood eosinophilia, LM and NP score values that detect CRSwNP patients needing ESS in a Finnish tertiary-care population.

Methods

Subjects

This retrospective follow-up study was carried out in the Departments of Otorhinolaryngology, at Tampere, Kuopio and Helsinki University Hospitals, and Päijät-Häme Central Hospital between 2001 and 2019. The study (nro 31/13/03/00/2015 and nro R07039) was approved by the ethical committee of the Hospital Districts.

Data of a total of 378 CRSwNP patients undergoing CRS surgical consultation at the Departments of Otorhinolaryngology between 2001 and 2019 was used. Inclusion criteria were: age >16 years, available patient record data of endoscopic nasal polyps during visit, and available data of ESS within one year after the consultation visit. CRSwNP was diagnosed according to the European Position Paper on CRS and nasal polyps (NPs).³²

The background data (age, gender, smoking habits, allergic rhinitis, asthma, NERD, previous ESS, baseline ESS) were collected from the hospitals' patient records. Asthma, NERD and AR diagnoses were based on self-reported doctor-diagnosed diseases. A doctor-diagnosed asthma is based on lung-function test results^{33,34} and a doctor-diagnosed AR is based on positive skin prick test and/or serum specific IgE results. NERD diagnosis was based on a positive history of wheeze/cough or naso-ocular symptoms after intake of NSAID, and in 97 patients NERD diagnosis was additionally based on a positive reaction (wheeze and/or naso-ocular reaction) after intake of ASA at the hospital.

Baseline ESS was defined as ESS that was performed within 12 months from the sinus CT scans and/or the baseline visit of sinus surgical consultation, which were on average one month apart. Previous ESS was defined as ESS that was performed before the baseline visit of sinus surgical consultation.

Three predictor variables were used. A.) The proportion of nasal polyp eosinophils of all leukocytes was collected from patient records or from the data of microscopically evaluated archival nasal polyp specimens as described.^{35,36} B.) LM score was evaluated from CT scans by ENT specialists³⁴ blinded to patient history data. C.) Endoscopic NP score and D.) Peripheral blood eosinophil count were collected from patient records. The eosinophilia, LM score and NP score were performed during the baseline visit before possible surgery, or at the surgery (NP eosinophilia).

The NP biopsy had been performed due to clinical purposes to confirm the pathologic diagnosis. The non-operated patients who were biopsied had undergone biopsy in local anesthesia at outpatient setting.

Statistics

Statistical analysis was carried out by the SPSS Base 15.0 Statistical Software Package (SPSS Inc., Chicago, IL, USA). Baseline ESS was used as endpoint. Associations were assessed by the Fisher's exact test (dichotomous) and differences in medians were studied by Kruskal-Wallis and Mann Whitney U test (continuous). The three variables were entered into a Receiver Operating Characteristic (ROC) curve. Predictive performance was assessed by the area under the receiver operating characteristic curve (AUROC). Two-tailed *P*-values of < 0.05 were considered statistically significant.

Results

Baseline Patient Characteristics

Of the total 378 patients, 192 (50.8%) were female, 165 (43.7%) had patient record history of AR, 248 (65.6%) had asthma, 182 (48.1%) had NERD, and 59 (15.6%) were current smokers. At baseline, median age (min–max) was 48.0 (17–89) years. A hundred and eighty-five (48.9%) of the patients did not have a patient-record history of previous ESS. 293 (77.5%) CRSwNP patients underwent ESS within a year after the consultation visit.

Comparison of CRSwNP Patients With and Without the Need of ESS

The operated CRSwNP group had a lower median age ($p < 0.001$) (Table 1). The other baseline factors (such as gender, smoking habits, co-morbidities, previous operations) did not differ between the groups (Table 1). The median value of polyp eosinophil proportion was

significantly higher in the operated CRSwNP group (Figure 1(A)), whereas the median total LM score of CT scans endoscopic NP score and blood eosinophil count did not significantly differ between the groups (Figure 1(B) to (D)).

Cut-off Values of Eosinophilia, LM- and NP-Scores

AUROC values (95% CI) for detecting those needing ESS were for polyp eosinophilia 0.71 (0.60–0.83), $p = 0.001$, for LM score 0.59 (0.50–0.67), $p = 0.054$; for NP score 0.56 (0.48–0.64), $p = 0.17$ and, for blood eosinophil count 0.68 (0.46–0.90), $p = 0.08$ (Figure 2). With the threshold value of polyp eosinophilia $> 25\%$, the sensitivity was 62% and specificity 71% for detecting the need for ESS. LM score had poor predictive potential. With the threshold value of LM score $\geq 4/24$ the sensitivity was 53% and specificity 56%. Similarly, endoscopic NP score had a poor predictive potential. With the threshold value of NP score $\geq 4/8$, the sensitivity was 69% and specificity 41%. Peripheral blood eosinophil count had good, yet statistically insignificant predictive potential. This might be due to low number of subjects ($N = 52$) with data available. With the threshold value of Blood eosinophil count $> 0.26 \times 10^9/L$, the sensitivity was 86% and specificity 60%.

Discussion

Finding the best predictors of primary surgery, revision surgery and uncontrolled disease, and including several relevant measures in prediction models has been proposed to increase possibilities of precision medicine in CRS.^{3,37} In this retrospective cross-sectional real-world study we wanted to observe radiological, endoscopic and pathological signs predicting patients undergoing ESS. We found that elevated nasal polyp eosinophilia, and to a smaller extent also higher LM score and endoscopic NP score predicted ESS, despite the fact that at the time when the study patients have been treated there have

Table 1. Patient History Data of the Chronic Rhinosinusitis With Nasal Polyps (CRSwNP) groups.

	Non-operated CRSwNP n = 85	Operated CRSwNP n = 293	<i>P</i>
Female, n (%)	37 (43.5)	155 (52.9)	.14
Age, median (Q1–Q3)	57.3 (43.8–64.2)	45.6 (35.3–55.7)	$< .001$
Current smoking, n (%)	15 (19.5)	44 (17.1)	.61
Allergic rhinitis, n (%)	30 (37.0)	135 (48.0)	.099
Asthma, n (%)	57 (67.9)	191 (67.3)	1.00
N-ERD, n (%)	39 (47.6)	143 (50.4)	.71
Number of previous ESS, median (Q1–Q3)	1 (0–3)	1 (0–2)	.11

CRSwNP patients at the time of undergoing consultation for baseline endoscopic sinus surgery.

NERD = patient-reported non-steroidal anti-inflammatory drug -exacerbated respiratory disease; *P* values by Fisher's exact test (dichotomous variables) or Mann Whitney U test (continuous variables). Q1 = 25% percentile, Q3 = 75% percentile.

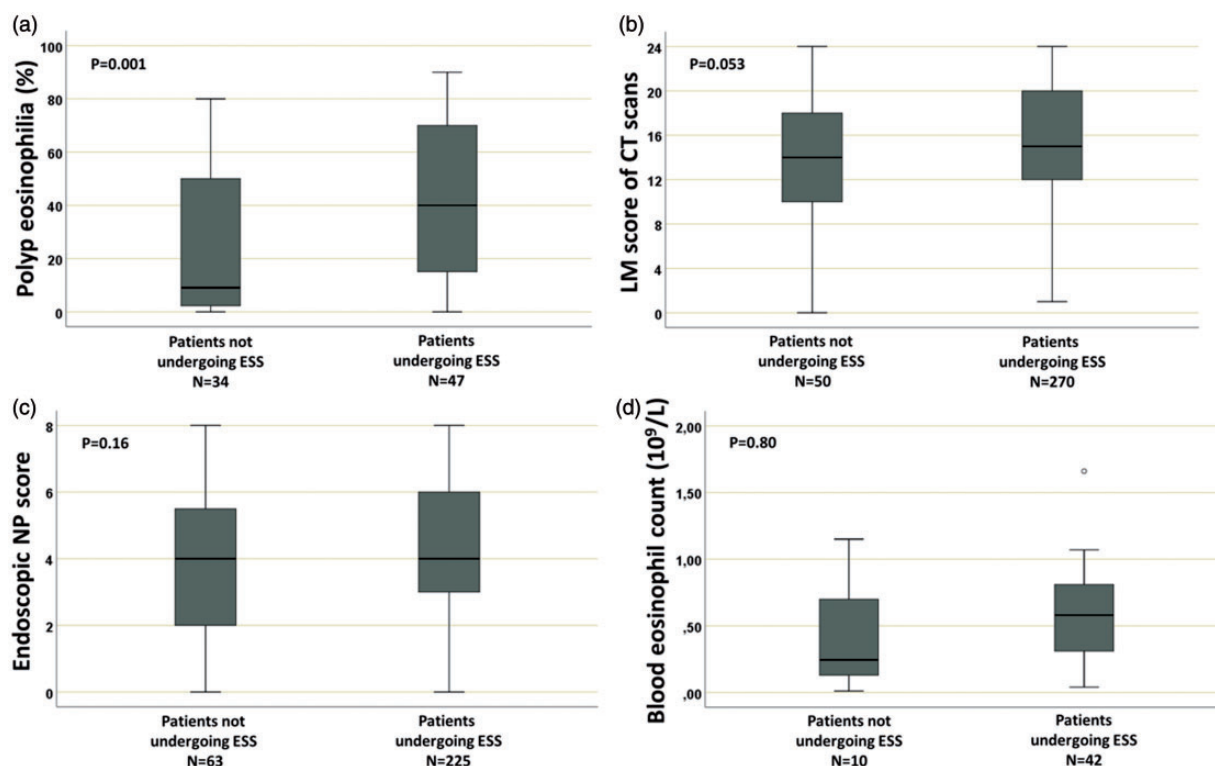


Figure 1. Comparison of the (A) polyp eosinophilia, (B) Lund-Mackay (LM) score of sinus computed tomography (CT) scans, (C) Endoscopic nasal polyp (NP) score, (D) Peripheral blood eosinophil count, in the chronic rhinosinusitis with nasal polyps (CRSwNP) patient groups. P-values by Mann Whitney U test.

been limited literature of predictive factors of uncontrolled CRS. Thus the importance of this study was to replicate the cut-off value of eosinophilia in a hospital CRS population, who has been treated at the time when ENT surgeon has not been yet fully aware of cut-off values of eosinophilia (or other markers) predicting uncontrolled disease.

We found that only NP eosinophilia was associated with proceeding to surgery in this clinical cohort of patients undergoing surgical consultation. The threshold of >25% of polyp eosinophils was optimal in prediction surgery, whereas NP score and LM scores were poor in predicting surgery. This finding is in line with previous studies from other countries/continents, showing that tissue eosinophilia predicts revision surgery and polyp recurrence, and it is also associated with more severe disease in CRSwNP.^{3,23–25,38,39} Recently, a recurrence rate of 48% was shown in patients with CRSwNP with mucosal eosinophilia using the EPOS definition for uncontrolled disease.^{1,24} Few studies have reported cut-off values of NP eosinophils for uncontrolled CRSwNP, whether defined by need for surgery, revision surgery or EPOS criteria for disease control. In a recent study with 136 Chinese CRS patients who had undergone ESS, a tissue eosinophilia value over 21% was found to be the best cut-off in prediction of uncontrolled CRS as

assessed by EPOS criteria.³ In a study of 387 Chinese CRSwNP patients the optimal cut-off percentage value of nasal polyp eosinophilia was 27% for predicting polyp recurrence in CRSwNP.³⁰ These findings are well in line with our results, as in our patients the cut-off value of >25% in nasal polyp eosinophilia had the best sensitivity and specificity for prediction of surgery in CRSwNP. Data of peripheral blood eosinophils was available only in small number of our patients. Nevertheless, we detected that peripheral blood eosinophil count had relatively good, yet statistically insignificant predictive potential and, the threshold value ($>0.26 \times 10^9/L$) was similar that has been reported in Chinese CRSwNP patients ($\geq 0.3 \times 10^9/L$).²⁹ Studies with increased subject number in different populations are still needed to evaluate the role of blood and polyp eosinophilia.

Results both for and against have been reported on the ability of LM CT score to predict surgical outcome.^{13,21,40–44} In a large prospective study LM CT score was shown to correlate with polyp grade, symptom reduction and to some extent with revision rates, but not with SNOT-22.⁴¹ No clear cut-off value in LM CT score for need of revision surgery could be found. The authors thought that LM CT score measures different aspects CRS severity than subjective measurements. Previous

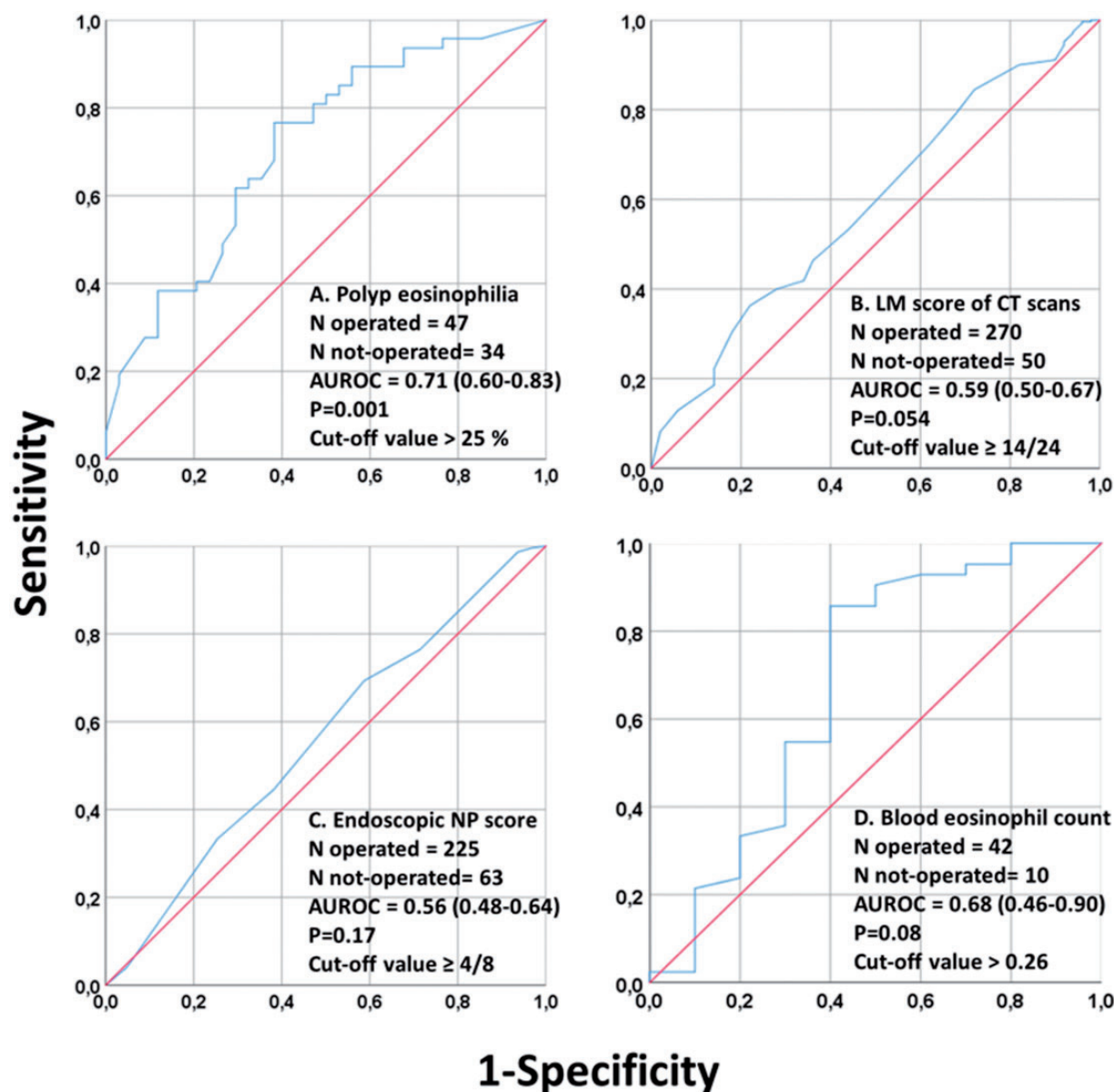


Figure 2. The Receiver operating characteristic (ROC) discrimination curve of prediction of endoscopic sinus surgery by (A) polyp eosinophilia, (B) Lund-Mackay (LM) score of sinus computed tomography (CT) scans, (C) Endoscopic nasal polyp (NP) score, (D) Peripheral blood eosinophil count. AUROC = area under the ROC curve. The values in parentheses indicate 95% confidence interval. A, Polyp eosinophilia had significant predictive potential. With the threshold value of polyp eosinophilia $>25\%$ the sensitivity was 62% and specificity 71% to predict CRS surgery. B, LM score had poor predictive potential. With the threshold value of LM score $\geq 14/24$ the sensitivity was 53% and specificity 56%. C, Endoscopic NP score had poor predictive potential. With the threshold value of NP score $\geq 4/8$ the sensitivity was 69% and specificity 41%. D, Peripheral blood eosinophil count had good, yet statistically insignificant predictive potential. This might be due to low number of subjects. With the threshold value of Blood eosinophil count $>0.26 \times 10^9/L$, the sensitivity was 86% and specificity 60%.

studies usually evaluate predictors of revision surgery, whereas half of our patients underwent primary surgery. It is possible that as indications for extensive surgery and revision have been poorly defined, limited surgery has often been the first choice at least for primary surgery and radiological severity has not been as important in the decision making of surgery. This may decrease the

prediction value of LM CT score in this study and perhaps in previous studies too.

CRS_{NP} is associated with recurrent disease more often than CRS_{NP}.⁴⁰ High polyp score may increase the risk for recurrent polyposis.²⁷ However, polyp score showed to be a poor predictor of ESS in this study. CRS symptoms and quality of life may have

been more important when considering surgery. The patient sample with both previously operated and unoperated patients may influence this finding.

The limitations of this study include limited number of patients having eosinophilia data, and the retrospective nature of the study, which may make clinical conclusions difficult to draw and emphasizes the need for prospective studies. The sample was not population-based as the patients were obtained from tertiary care. Due to the retrospective nature of this study, we could not confirm the EPOS diagnostic criteria. We acknowledge that lack of patient-reported outcome measure (e.g., SNOT-22), and lack of some other factors that have previously been published as criteria of uncontrolled CRSwNP^{1,32} which limits the interpretation of the findings. On the other hand, due to retrospective nature of the study the clinicians who had treated these patients were blinded to the results. We acknowledge that in this real-world setting several factors have affected the operation decision-making and they might have included to some extent also variables that were of our interest. Yet literature-proven cut-off values were not available or used at that time. Our analysis of surgery may have been influenced by factors unrelated to recurrence of CRS, including waiting times for surgery and patients' preferences to delay surgery for personal reasons. Other factors that can also affect the timing of surgery include the patients' tolerance of rhinosinusitis symptoms, the operative technique used at the time of the initial surgery, and the surgeon's opinion as to when revision surgery is clinically warranted.

Conclusion

This study demonstrated good prediction for need of surgical treatment in CRSwNP with >25% nasal polyp eosinophilia. The role of LM score and polyp score was not as obvious in this patient sample. Prospective studies in different populations are still needed.

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Declaration of Conflicting Interests

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ORCID iDs

E. Penttilä  <https://orcid.org/0000-0002-4818-2734>

A. Laulajainen-Hongisto  <https://orcid.org/0000-0001-5109-6944>

M. Lilja  <https://orcid.org/0000-0003-1781-1718>

S. Toppila-Salmi  <https://orcid.org/0000-0003-0890-6686>

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